

# Epigenetics and multiple risk factors in development: Perspectives from autism research

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**UC Davis Genome Center**



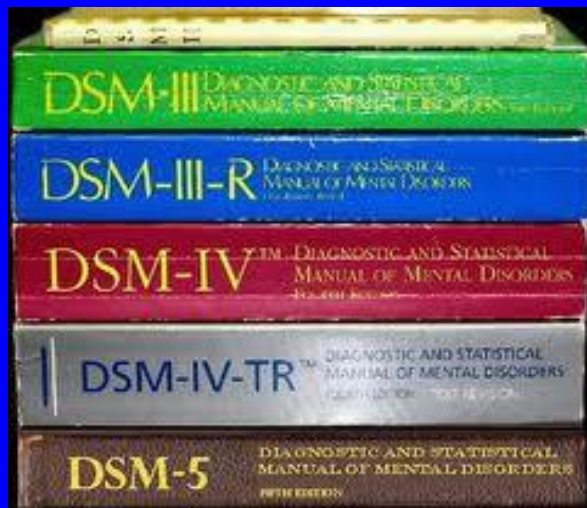
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# Autism spectrum disorders



- Complex developmental disorder that usually appears in first three years of life
- Not a single disorder but a spectrum of neurodevelopmental disorders characterized by:
  - Impairments in social interactions and communication
  - Impairments in language
  - Restrictive and repetitive interests and behaviors



Challenge for research: Changing diagnoses and lack of molecular tests

DSM IV to DSM V: one heading termed “Autism Spectrum Disorders”

# Genetics of autism spectrum disorders and the ongoing nature vs. nurture debate

## Heritability estimates of Autism

### Twins

90% based on a small monozygotic versus dizygotic twin study in 1960s (Steffenberg et al, 1989)

70-90% from a variety of larger twin studies pre-2010

38% based on 2011 study that separated calculated effect of shared in utero environment (58%) (Hallmayer et al, 2011)

### Siblings

50-100x greater risk for sibs of children with autism compared to the general population

Most recent and largest family analysis from a population of 2 million in Sweden put estimate of 50% heritability, suggesting a 50% “environmental” or non-genetic component

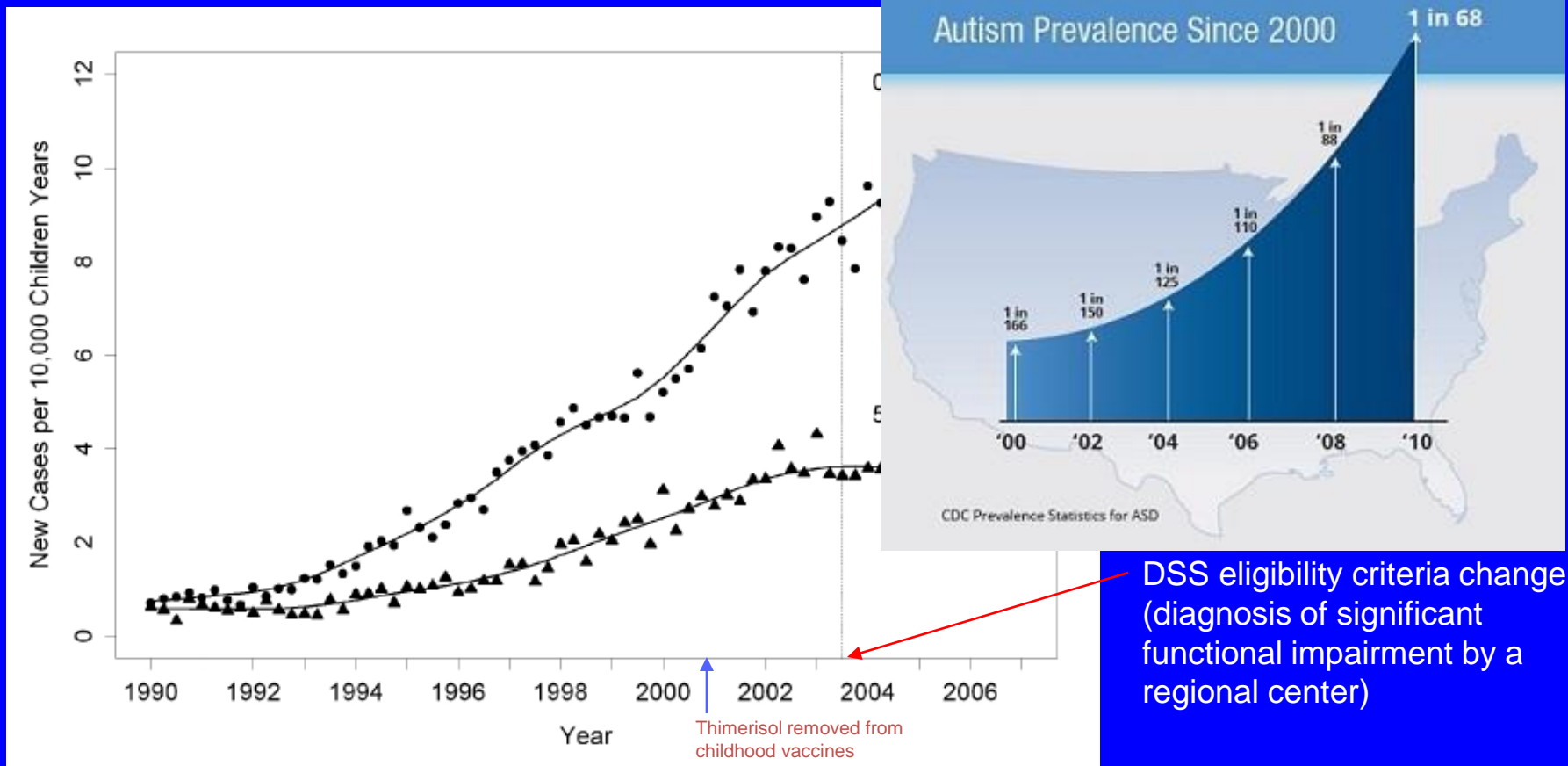
## ASDs are complex genetic disorders

Multiple known genetic causes of ASD, but each contribute to at most 1% of ASDs

# Is autism incidence on the rise?

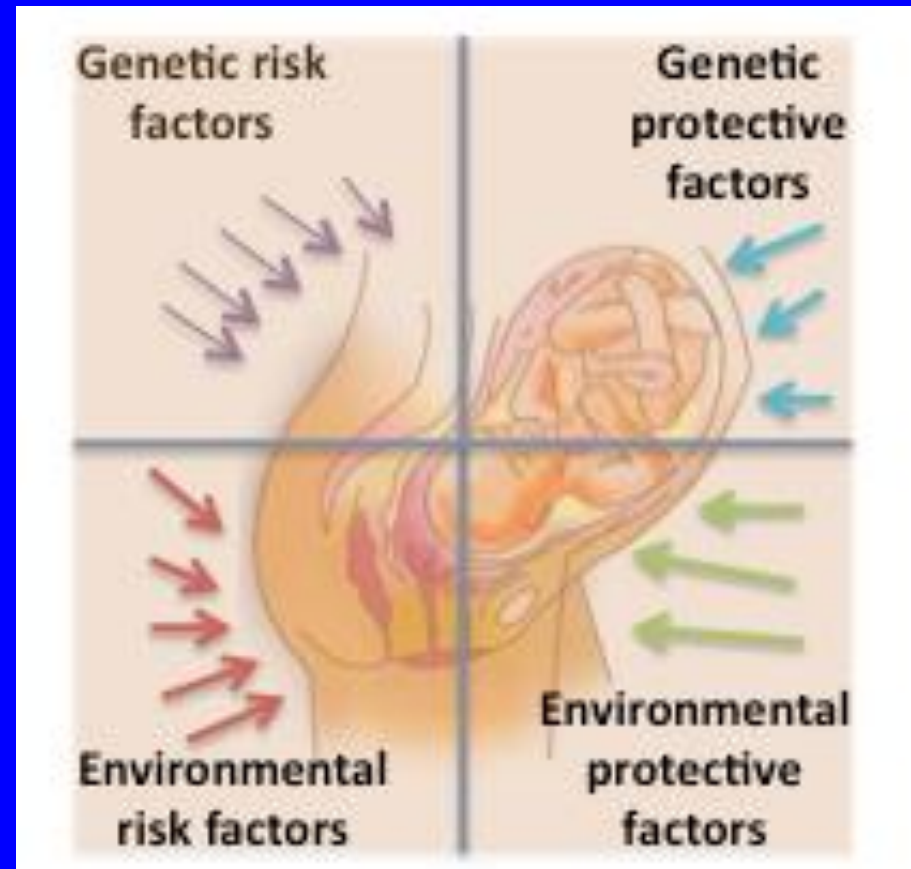
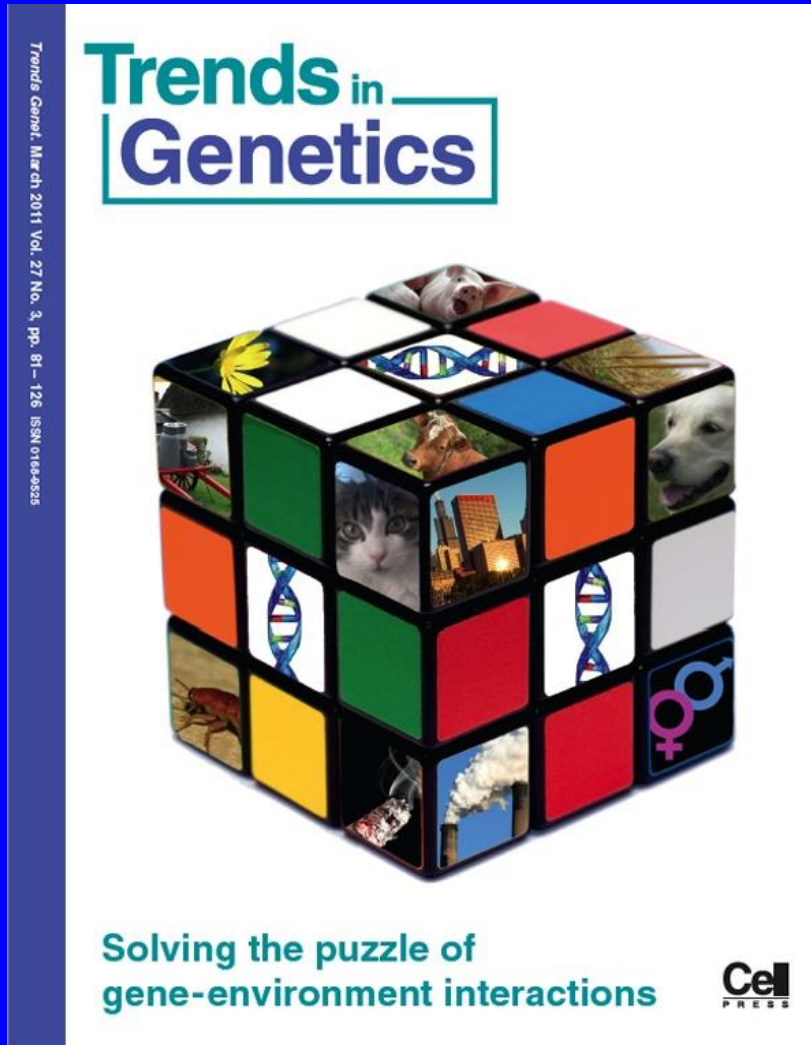
California's Developmental Services System

Hertz-Picciotto and Delwiche, *Epidemiology*, 2009

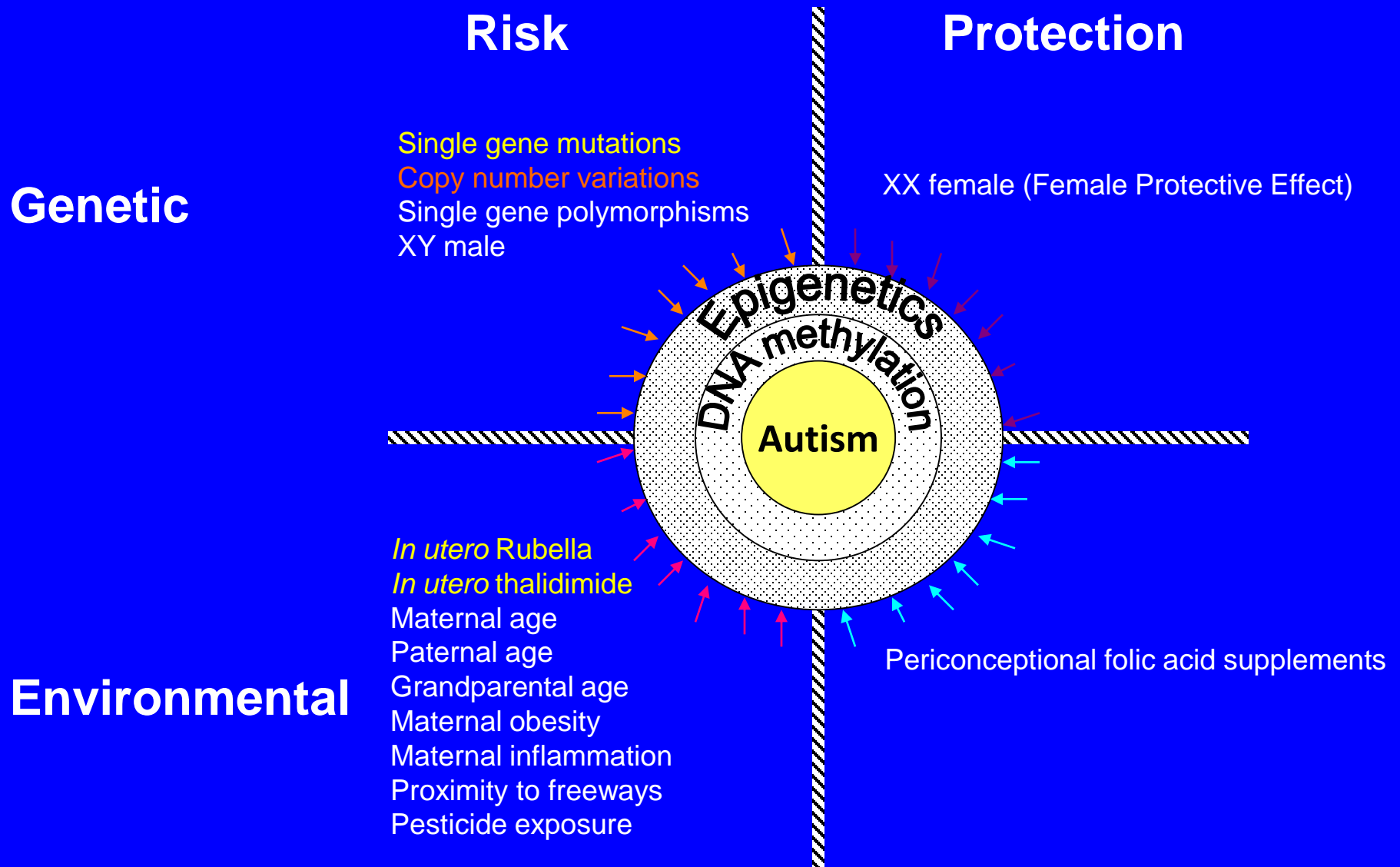


Only 200% of the 600% increase can be explained by increased diagnosis

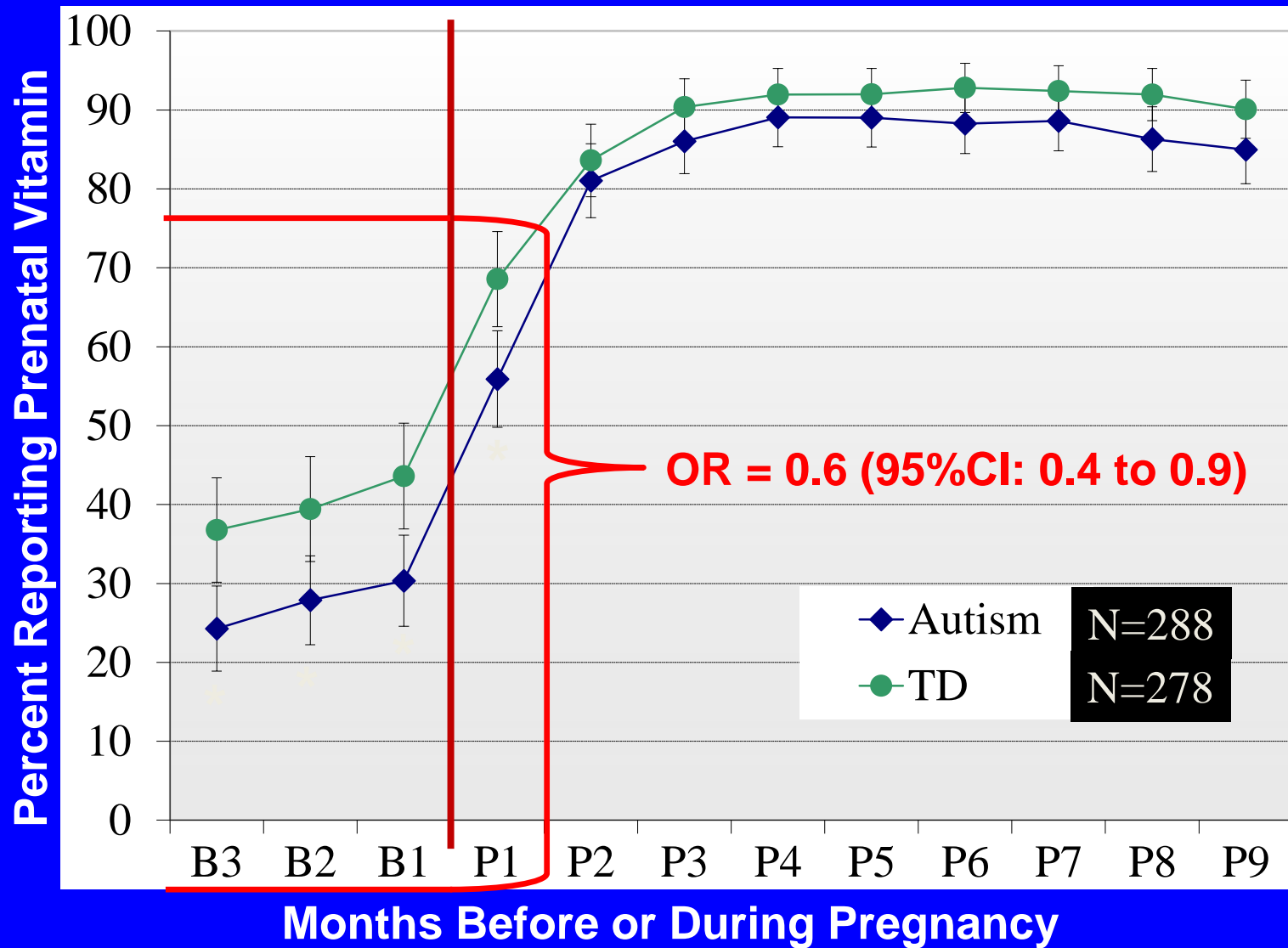
# Gene x environment interactions in autism risk



# Epigenetic mechanisms act at the interface of genes and the environment



# Prenatal Vitamin Use by Perinatal Month



# Absence of folic acid at conception modifies autism risk with multiple environmental exposures

data from the CHARGE case-control study

Environmental Exposure During Pregnancy		800+ mcg FA Preg Month 1 aOR (95% CI)	<800 mcg FA Preg Month 1 aOR (95% CI)
Traffic-Related Air Pollution (Total Nox)	No	Reference	1.21 (0.77-1.88)
	Yes	1.25 (0.79-1.98)	<b>2.11 (1.33-3.33)</b>
Any Exposure to Sprays/Foggers	No	Reference	1.41 (0.96-2.07)
	Yes	<b>1.65 (1.06-2.55)</b>	<b>2.67 (1.62-4.42)</b>
Regular Use of Sprays/Foggers (6+ months)	No	Reference	1.39 (0.99-1.96)
	Yes	<b>2.27 (1.29-4.00)</b>	<b>4.99 (2.25-11.06)</b>
Pregnancy Chlorpyrifos	No	Reference	1.28 (0.93-2.01)
	Yes	0.75 (0.36-1.55)	2.24 (0.80-6.32)
Pregnancy Organophosphates	No	Reference	1.23 (0.87-1.74)
	Yes	0.87 (0.51-1.50)	<b>1.89 (1.03-3.48)</b>
Pre-conception Pyrethroids	No	Reference	1.36 (0.98-1.89)
	Yes	0.95 (0.45-2.00)	<b>3.70 (1.23-11.13)</b>



**MARBLES**

# MARBLES

## Markers of Autism Risk in Babies: Learning Early Signs

400 Mothers of a child with autism planning pregnancy or pregnant with another child

Recurrence rate is ~ 1 in 5 (Ozonoff et al 2011)

**Pregnancy**

**Child Neurodevelopment**

**Final Dx**

**EEQ, FFQs**



**Biologic Samples**

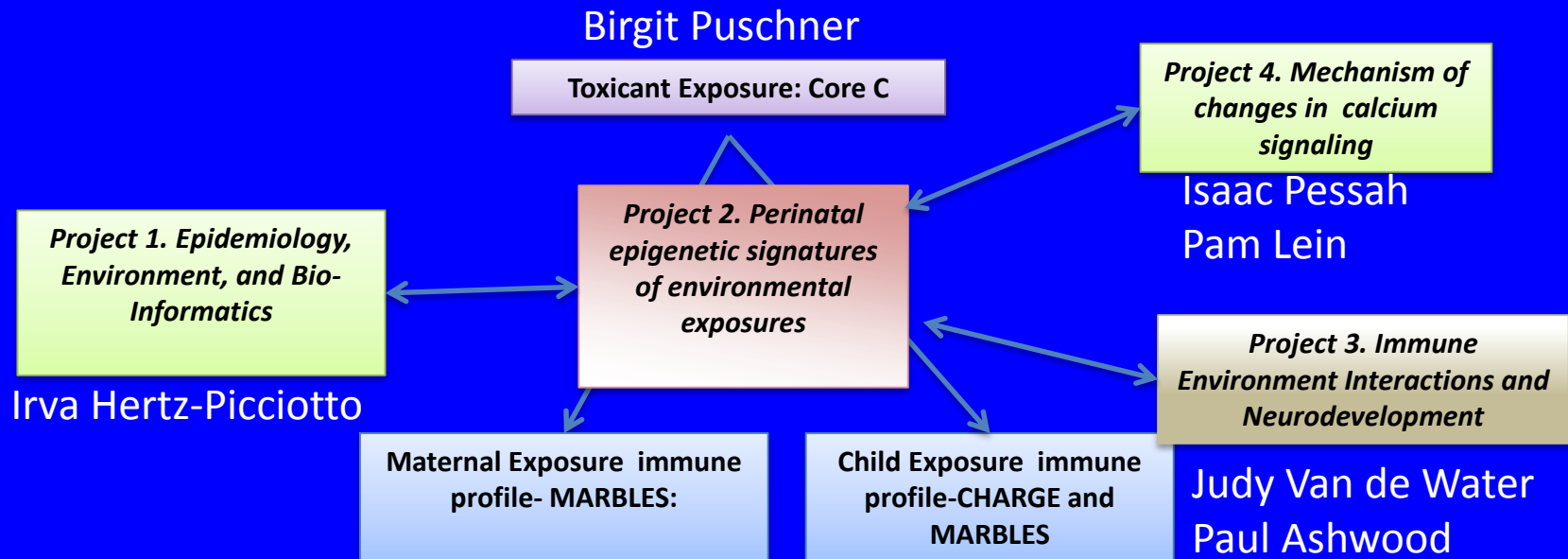


**Parent Forms & Clinical Assessments**



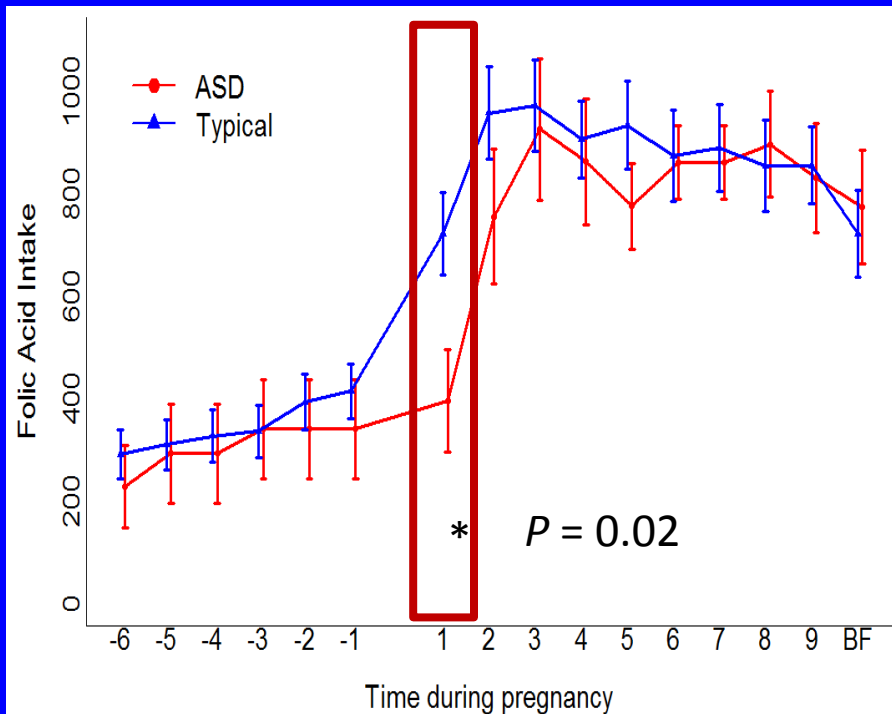


# CCEH Project 2- Center interactions

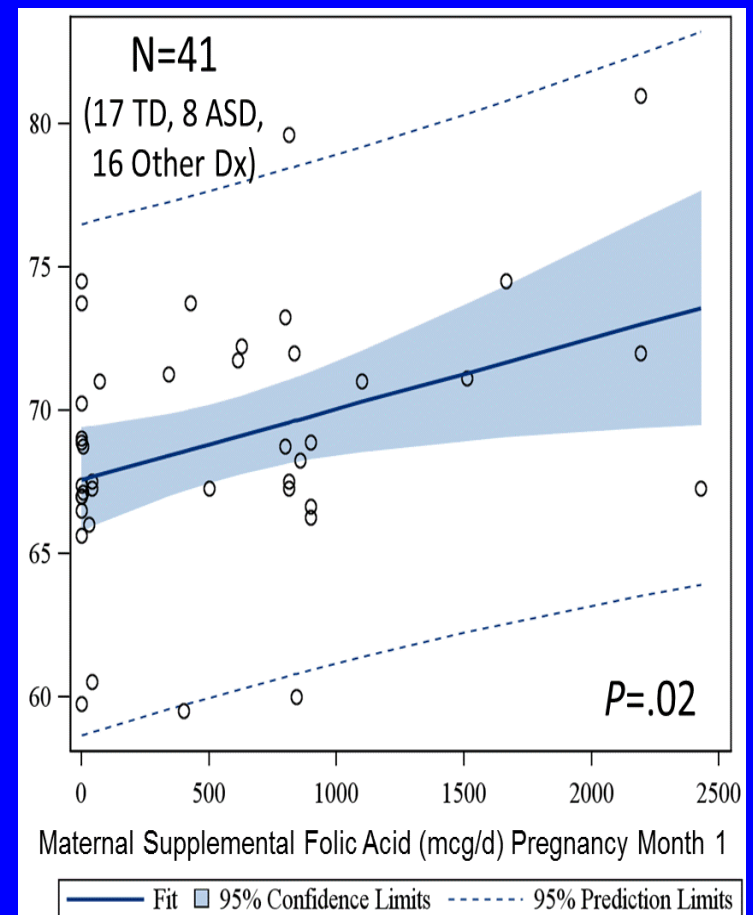


# MARBLES analysis of folic acid protection and global DNA methylation

## Folic Acid Intake (mcg): By Month

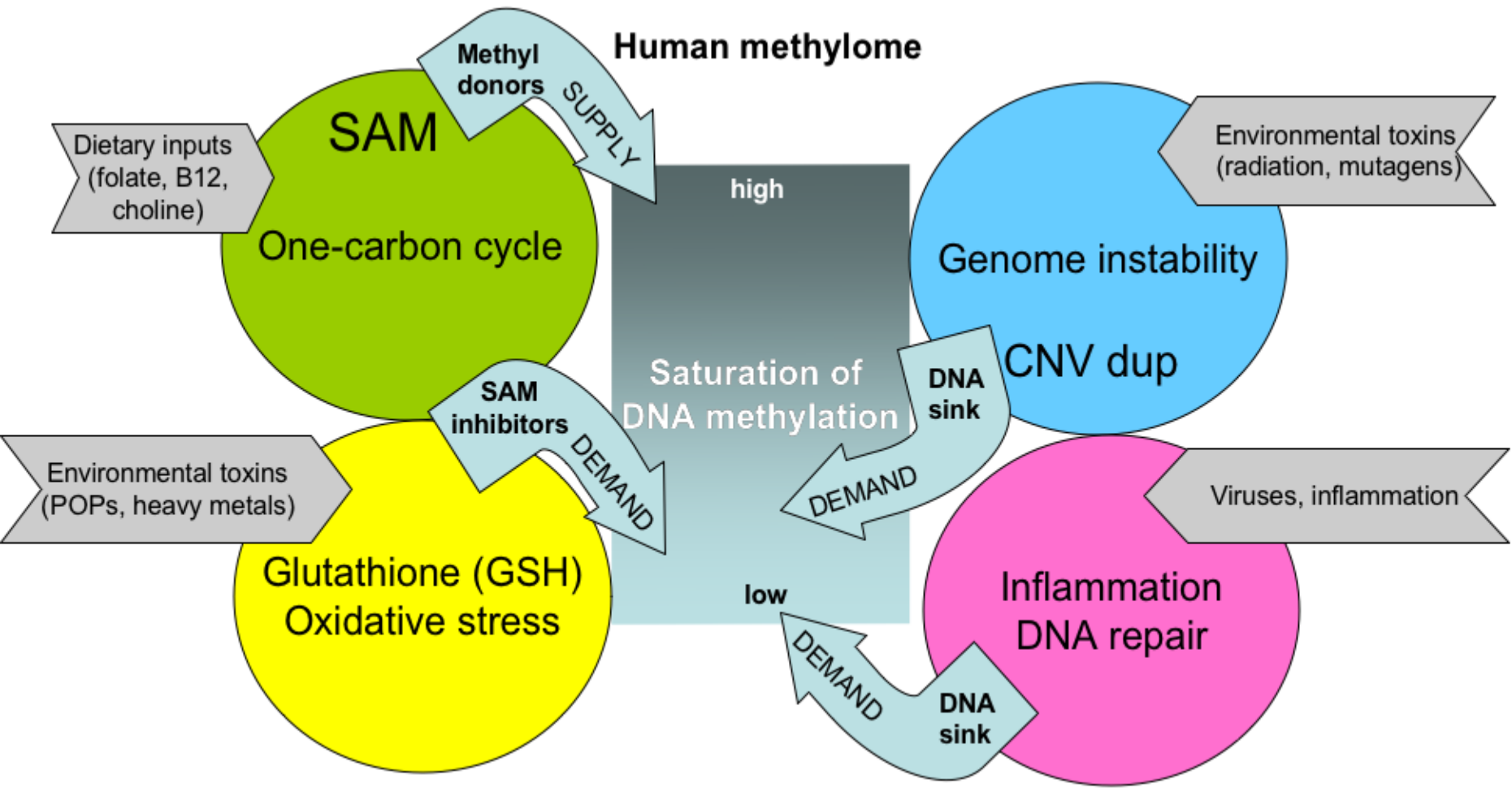


## LINE1 DNA methylation by Folic Acid



# Environmental impacts on the brain methylome

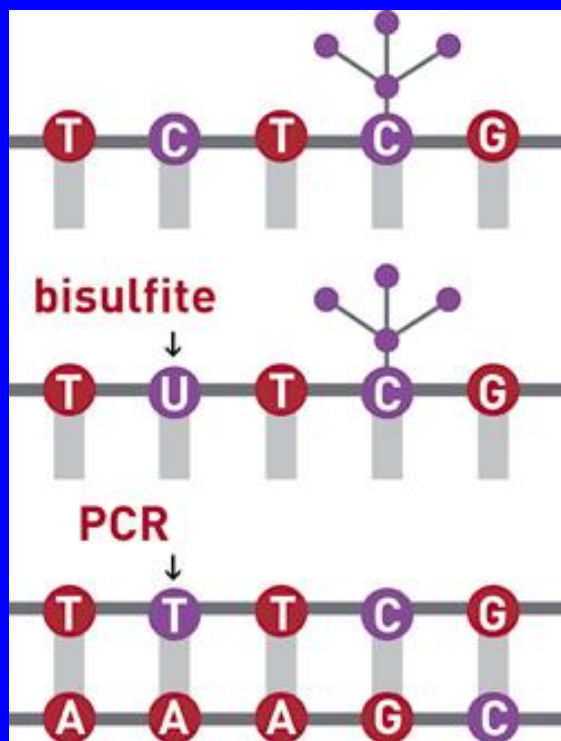
## An integrative genome point-of-view



## Apply genomic and bioinformatic tools to investigate MARBLES placenta and cord blood samples

- Assess the global impact on DNA methylation over partially methylated domains and repeats
- Find specific differentially methylated regions with associated with environmental exposure and/or ASD diagnosis

### Methyl-C Sequencing



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**UC Davis Genome Center**



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## Collaborators, UCD

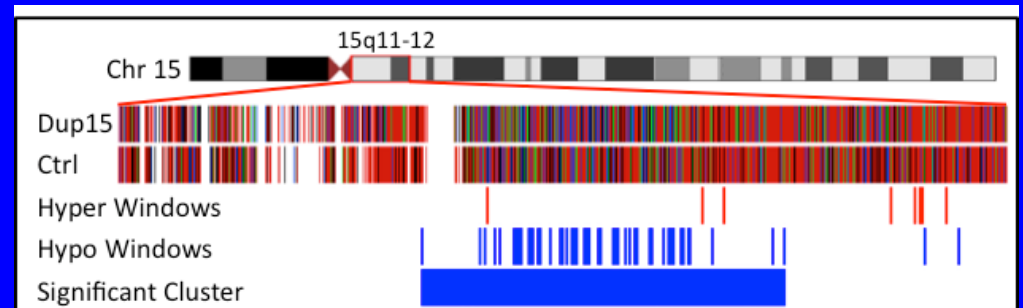
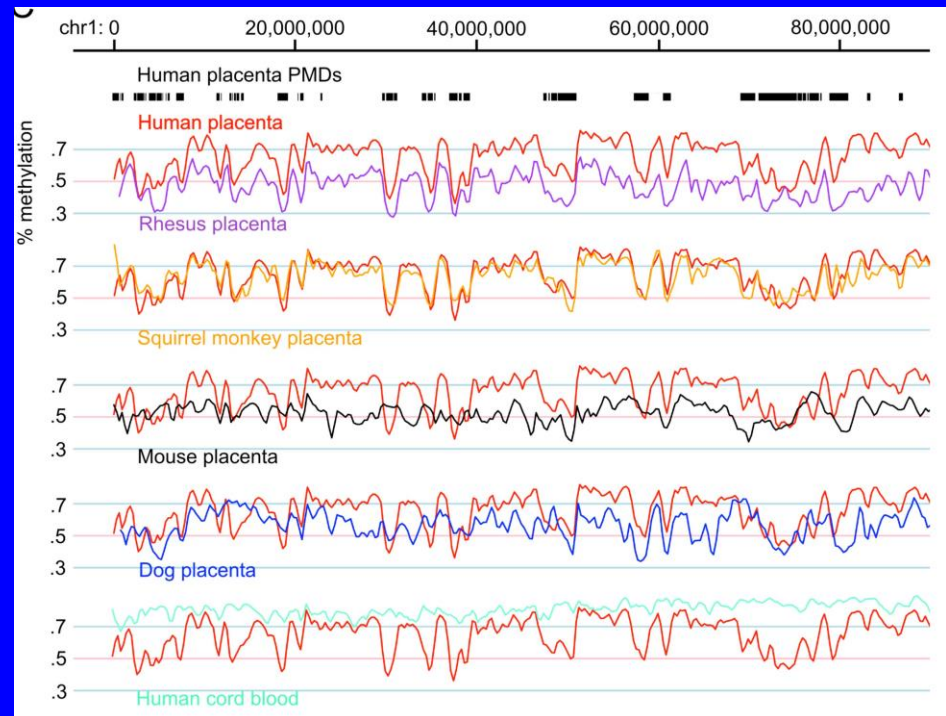
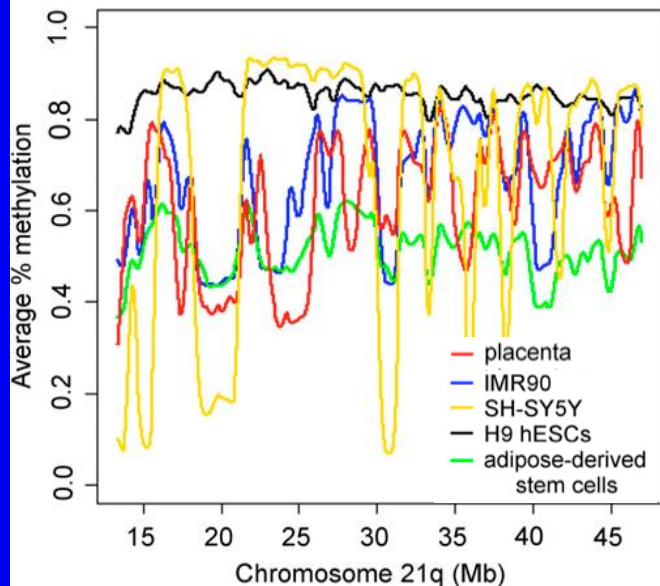
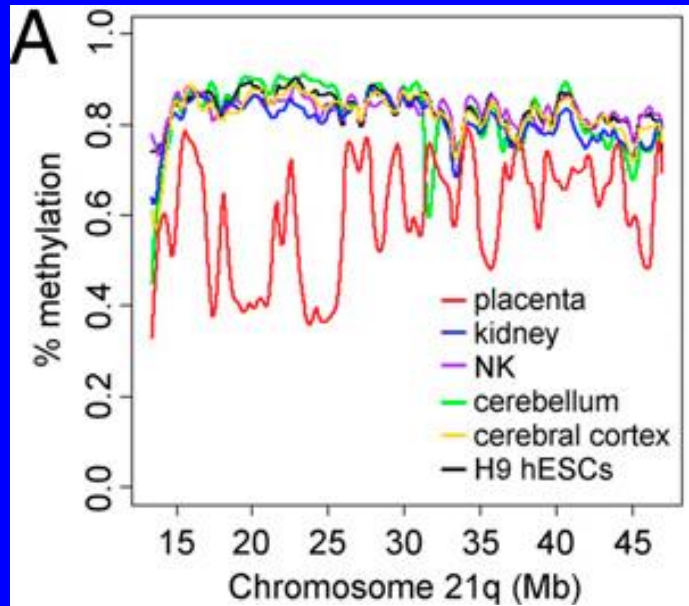
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# Mapping the methylome in brain and placenta

The landscape feature of partially methylated domains in early life



# Prenatal vitamin protection in MARBLES

Prenatal Vitamin ≤ P1	<u>ASD</u> N (%)	<u>Typical</u> N (%)	RR (95% CI)	<i>P</i>	<sub>adj</sub> RR* (95% CI)	<i>P</i>
Yes	5 (24)	42 (62)	Reference			
No	16 (76)	26 (38)	3.7 (1.5, 9.1)	<b>.005</b>	4.0 (1.5, 10.0)	<b>.003</b>

# MARBLES

## Plasma:

422 Homocysteine  
127 mothers, 19 children

## Homocysteine

**Nutrient  
Status**

**DNA  
Methylation**

**Child  
Neurodevelopment**

**Completed  
Visits**  
130 36-month

**Folate  
B-Complex  
Vitamins**

**Autism, ASD  
Other Neurodevelopmental  
Outcomes**

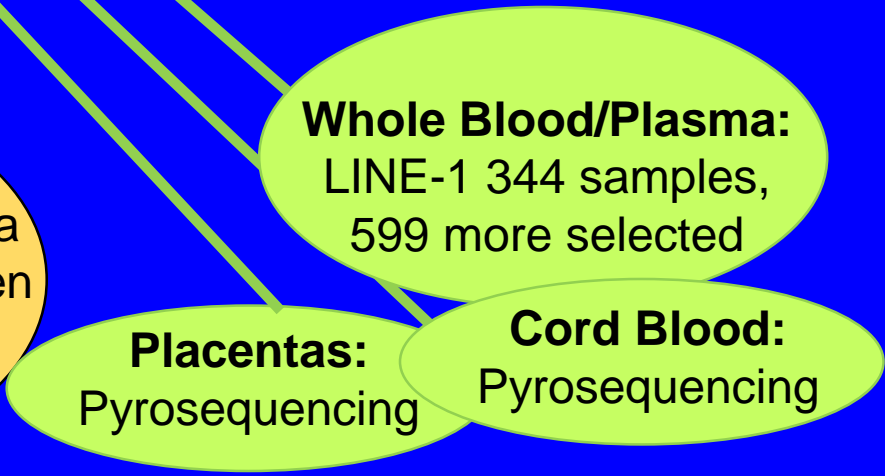
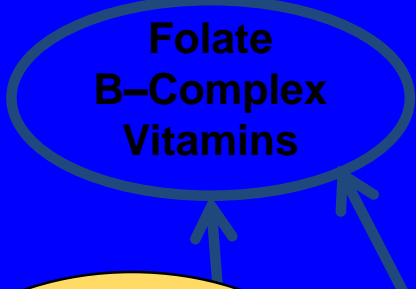
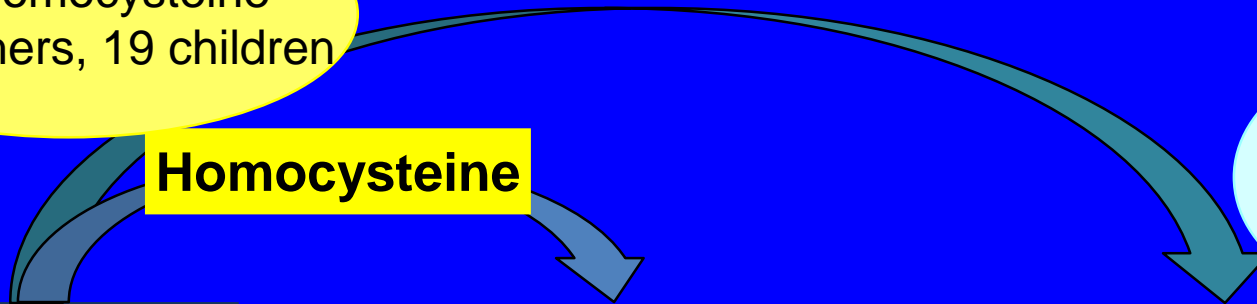
**Food Frequency  
Questionnaires:**  
184 Analyzed  
Folate, B12, B6,  
choline, Hcy

**Serum/Plasma:**  
432 serum, 422 plasma  
127 mothers, 19 children  
Folate, B12, B6,  
Choline, Hcy

**Whole Blood/Plasma:**  
LINE-1 344 samples,  
599 more selected

**Placentas:**  
Pyrosequencing

**Cord Blood:**  
Pyrosequencing



# MARBLES

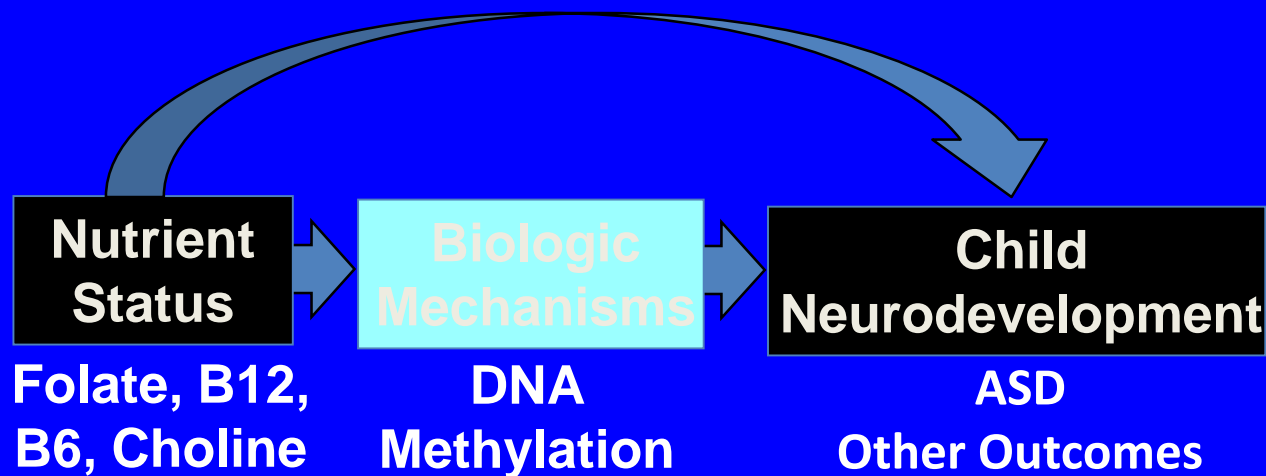
## Markers of Autism Risk in Babies: Learning Early Signs PI: Irva Hertz-Picciotto

400 Mothers of a child with autism planning pregnancy or pregnant with another child

FFQs



Maternal & Child Serum



Parent Forms and Clinical Assessments

